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## Questions regarding the optimal use of bevacizumab in glioblastoma: a moving target

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The saga of bevacizumab in brain tumors has been ongoing for many years. Despite encouraging initial reports targeting the vascular endothelial growth factor (VEGF) pathway by a neutralizing monoclonal antibody (bevacizumab) or a receptor tyrosine kinase inhibitor (cediranib), the few subsequent controlled studies were largely disappointing. Opportunities for adequate clinical investigation with bevacizumab were missed or delayed for many years. Nevertheless, these agents undoubtedly have a clinically meaningful benefit in selected patients. However, we lack clinical or biomarkers allowing identification of specific patients that benefit from these therapies. The highly variable clinical practice reflects the contradictory reports and the paucity of prospective and controlled trials. The absence of adequate data also prevented regulatory approval in many countries, especially in the European Union, thus preventing access to bevacizumab for patients. Numerous basic questions remain unresolved years after the drug has entered routine clinical use.<sup>1</sup> Two reports analyzing retrospectively large institutional databases on management of recurrent glioblastoma appear in this issue of *Neuro-Oncology*,<sup>2,3</sup> and two pivotal prospective randomized trials on the use of bevacizumab in newly diagnosed patients were recently reported.<sup>4,5</sup> Thus, it is timely to briefly review some of the available data and discuss their limitations.

### Dose and schedule

In 2005, a practicing oncologist from Texas first reported the use of bevacizumab for recurrent glioma. She treated 21 patients with a standard regimen of bevacizumab (5 mg/kg every other week) and irinotecan (125 mg/m<sup>2</sup> weekly) at doses previously established for colorectal cancer and observed 9 responses and 11 disease stabilizations.<sup>6</sup> For unclear reasons, in subsequent trials a lower dose of irinotecan (125 mg/m<sup>2</sup> every other week) was used while the bevacizumab dose (10 mg/kg) was doubled.<sup>7</sup> At the same time the randomized AVAIL study showed that increasing the dose of bevacizumab from a low 2.5 to 5 mg/kg per week (7.5 mg/kg and 15 mg/kg q 3 weeks, respectively) failed to improve outcome in non-small cell lung cancer.<sup>8</sup> Bevacizumab's long terminal half-life of 21–27 days would allow for dosing intervals of 3–4 weeks or longer. Some preclinical models suggest that high doses of anti-angiogenic therapy may be detrimental by inducing hypoxia and induce a more aggressive and invasive

phenotype;<sup>9–11</sup> although, in one murine model, higher doses of bevacizumab conferred a longer survival.<sup>12</sup>

### Should bevacizumab be given in combination with a cytotoxic agent?

Bevacizumab was the first anti-angiogenic and vasculature-modifying agent entering the clinic in the treatment of solid tumors. As a single agent it was without activity<sup>13</sup>; however, in combination with cytotoxic chemotherapy (irinotecan/5-fluorouracil) it prolonged survival in recurrent colorectal cancer,<sup>14,15</sup> and in combination with cytotoxic therapy some activity has also been demonstrated for non-small cell lung cancer, breast cancer, and ovarian cancer. Thus, there is a strong, indirect rationale to combine bevacizumab with cytotoxic chemotherapy in glioma. The non-comparative randomized phase II BRAIN trial examined bevacizumab alone and bevacizumab with irinotecan.<sup>7</sup> Progression-free survival was somewhat prolonged with the combination, but there was no difference in overall survival. Irinotecan is not an accepted active agent for recurrent glioblastoma, however. We lack truly active second-line cytotoxic chemotherapy after temozolomide failure. The REGAL trial in recurrent glioblastoma was a randomized phase III trial comparing cediranib (VEGFR-tyrosine kinase inhibitor (TKI) or the combination of cediranib and lomustine (CCNU) with lomustine alone.<sup>16</sup> The two lomustine-containing arms showed a trend towards improved outcome over cediranib alone; however, the combination of cediranib and lomustine was not superior to lomustine alone. In a small, Dutch randomized phase II trial improved survival was suggested with the combination of bevacizumab and lomustine vs lomustine or bevacizumab alone.<sup>17</sup> This regimen is currently being evaluated in a definitive phase III trial by the European Organisation for Research and Treatment of Cancer (EORTC trial 26101, NCT#01290939). Thus, among a plethora of agents tested in uncontrolled trials, only lomustine has provided a signal of activity in combination with bevacizumab, and interestingly, lomustine stands out somewhat by its intrinsic activity in the recurrent setting. Of note, the combination of anti-angiogenic agents with other pharmacological agents may require careful, preferentially early sequencing studies, since the vascular normalization paradigm is increasingly challenged and drug delivery may indeed be inhibited by drugs like bevacizumab.<sup>18</sup>

# When and for how long should bevacizumab be given?

In this issue of Neuro-Oncology, Piccioni et al interrogated their database of 468 patients treated with standard temozolomide (TMZ) and radiotherapy (RT)<sup>19</sup> who received bevacizumab upfront or at the first or a later recurrence.<sup>3</sup> Progression-free survival after bevacizumab initiation of 4 months was similar whether bevacizumab was initiated at first recurrence or at a later stage, leading the authors to conclude that administration can safely be deferred to a later stage in relatively asymptomatic patients. Similarly, combination with a cytotoxic agent did not improve survival.

Puduvalli and colleagues report on their experience on 82 patients with recurrent glioblastoma who were responding or stable on bevacizumab therapy for more than 6 months.<sup>2</sup> In 18 patients bevacizumab was discontinued early for reasons other than disease progression (eg toxicity, patient's refusal) and the results with these patients were compared with those of the 64 patients who continued treatment until progression or beyond. Time to progression after bevacizumab discontinuation was 27 weeks. Importantly, at subsequent progression a sustained response was obtained again in almost half of the patients (median PFS6 47% [95%CI 23-94%], while only 5% of the patients who progressed while receiving bevacizumab achieved subsequent disease stabilization with salvage therapy (median PFS6 5% [95%CI:1-21%]).

Preclinical data suggested synergy when bevacizumab was combined with radiation. Two independent but similarly designed randomized trials (AvaGlio, designed and sponsored by Roche/Genentech, and RTOG0825, developed by the Radiation Therapy Oncology Group) evaluated bevacizumab when given to newly diagnosed glioblastoma patients in conjunction with radiotherapy and temozolomide. Bevacizumab was given from day 1 of TMZ/RT (AvaGlio) or starting in the fourth week of TMZ/RT (RTOG trial) at a dose of 10 mg/kg every other week and was to be continued until disease progression. Progression-free survival was prolonged in both trials in the bevacizumab arms (median 10.7 vs 7.3 months in RTOG0525; 10.6 vs 6.2 months in AvaGlio); however, this did not translate into prolongation of overall survival. Importantly, the median overall survival of 16 months is not substantially longer than the overall survival in prior TMZ-containing trials. And despite the use of bevacizumab either upfront or at recurrence, survival is comparable also to the pivotal EORTC/NCIC trial<sup>19,20</sup> conducted almost 10 years earlier which also included biopsy-only patients (in the RTOG trials surgical tumor debulking was mandatory). One may conclude that bevacizumab does not substantially increase survival in glioblastoma, whether given upfront or at recurrence. To date, no subgroup has been identified that consistently benefits from VEGF inhibition, although elderly patients may derive relatively more benefit.<sup>21</sup>

But isn't a prolongation of progression-free survival a valuable benefit in patients where disease progression is commonly associated with debilitating neurological symptoms? Unfortunately, there is uncertainty in determining progression based on radiological findings alone, in the absence of clinical progression, when using an agent that interferes with vessel permeability and contrast enhancement. There is also uncertainty in the effects of bevacizumab on quality of life. Conclusions about quality of life (AvaGlio) and net clinical benefit (RTOG0825) are contradictory. While quality of life appears improved due to the delayed progression in the experimental arm in AVAGlio, bevacizumab appeared to decrease net clinical benefit (a composite of quality

of life and neurological function) in the RTOG study. A limitation of both studies is that they discontinued evaluation of secondary endpoints and quality of life at the time of tumor progression, when evaluation of quality of life should ideally also cover the period post-progression.

Controversy persists regarding whether bevacizumab should be discontinued upon progression. Due to the lack of efficacious salvage treatments and the fear of rebound, treatment with bevacizumab is commonly maintained beyond progression. There is no data supporting this practice and the long half-life of bevacizumab makes this a priori unlikely. Nevertheless, a rebound in contrast enhancement and edema may be observed with the waning effect of bevacizumab 6–8 weeks after discontinuation, making evaluation of efficacy of subsequent treatments challenging. Conversely, rapid rebound within hours to days due to the short half-life of VEGFR-TKI have been observed.<sup>16,22</sup> Little clinical benefit has been demonstrated with adding another cytotoxic agent while continuing bevacizumab beyond progression.<sup>7,23,24</sup> The ongoing Roche-sponsored randomized phase III TAMIGA trial is evaluating the value of continuation of bevacizumab for patients who have progressed following first-line therapy with bevacizumab and TMZ/RT vs TMZ (NCT#01860638).

In summary, we have made only very modest progress in the management of glioblastoma over the last decade. A series of prospective randomized trials failed to demonstrate significantly improved outcome.<sup>4,5,16,25–27</sup> Bevacizumab and other VEGF pathway inhibitors have consistently resulted in radiological reduction in contrast enhancement, and peritumoral edema allowed for a decrease in corticosteroid requirement.<sup>7,16,23</sup> Nevertheless, short of adequate clinical investigations we remain unable to identify patients likely to benefit from bevacizumab. The commonly used high doses of bevacizumab are associated with some, albeit limited, toxicities, that may have contributed to the negative results in newly diagnosed patients with increased side effects and a decrease in net clinical benefit. There may be value in reduced utilization of corticosteroids and their inherent toxicity; however, potential benefits related to reduction in steroids and improvement in quality of life have never been investigated. Strategic errors and omissions in a drug's early developmental plan are difficult to correct years later. Requirements needed for regulatory approval may not match the clinical reality of the use of a drug already on the market. The retrospective investigations by Piccioni and Puduvalli and other anecdotal experience suggest that bevacizumab should be used at a later time point in the course of the disease,<sup>3</sup> administered for a shorter time (e.g. 6 months only),<sup>2</sup> and possibly at a lower dose,<sup>12</sup> at least for the majority of patients who are eligible for more than one line of treatment.

**Conflict of interest statement.** R.S. and M.W. have served on advisory boards for Roche/Genentech, Merck-Serono, MSD/Merck & Co.

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